

## **REMARKS**

Claims 1-4 were pending and under consideration in the present application. With this amendment, Claims 5-9 are added. Thus, following entry of the instant amendment, Claims 1-9 are currently pending and under consideration. A marked-up copy showing amendments to the claims is presented in *Appendix A*. The currently pending claims are presented in *Appendix B*.

### **I. The Amendments to the Specification**

The specification has been amended in order to correct minor informalities in the specification and to more clearly identify the four panels of Figure 6. Applicants respectfully submit that the amendments to the specification cure the deficiencies noted by the PTO in the outstanding Office Action. Entry of the amendments to the specification under 37 C.F.R. §1.111 is hereby respectfully requested.

### **II. The Amendments to the Claims**

The Claims have been amended, without prejudice, in order to more clearly point out and distinctly claim that which Applicants regard as their invention. Specifically, Claims 1 and 4 have been amended, and new Claims 5-9 have been added. The amendments do not introduce new matter and they are fully supported by the specification of the present application and the claims as originally filed.

In particular, Claims 1 and 4 have been amended to correct minor errors in claim language. Support for the amendment to Claim 1 may be found at, for example, page 4, lines 10-14 and Claim 1 as originally filed. Support for the amendment to Claim 4 may be found at, for example, page 6, lines 17-18, and Claim 4 as originally filed.

New dependent Claim 5 recites Taq DNA polymerase and Pwo DNA polymerase as the two polymerases of Claim 1. New dependent Claim 6 recites a sample of cells as the sample of Claim 1. New dependent Claim 7 recites treating said sample of cells with a protease prior to the two thermocyclic amplification reactions recited by Claim 1. New dependent Claim 8 recites proteinase K as the protease of Claim 7. New independent Claim 9 recites a method similar to that of Claim 1, while further requiring that in the first amplification reaction, the temperature at which primer extension is carried out is increased in at least some of the successive amplification cycles.

Support for new Claim 5 may be found at, for example, page 6, lines 1-4. Support for new Claims 6-8 may be found at, for example, page 6, lines 8-11 and page 10, lines 24-26. Support for new Claim 9 may be found at, for example, page 5, lines 9-15.

Entry of the amended claims under 37 C.F.R. §1.111 is hereby respectfully requested.

### **III. The Oath or Declaration of the Inventors**

The PTO has objected to the oath or declaration, alleging it to be defective as failing to acknowledge the duty of disclosure under 37 C.F.R. § 1.56. The PTO's attention is respectfully invited to the Declaration and Power of Attorney filed February 28, 2002, together with the present Application and Sequence Listing, at page 1, approximate line 17. Here, the Declaration contains an acknowledgment of the duty of disclosure pursuant to 37 C.F.R. § 1.56. Thus, the declaration does contain such an acknowledgment and accordingly is not defective as alleged by the PTO. Applicants kindly solicit recognition of the same.

### **IV. The Rejections**

#### **A. The Rejection of Claims 1-4 Under 35 U.S.C. § 112, Second Paragraph**

Claims 1-4 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Applicants respectfully submit that the rejection is obviated in view of the amendment to the claims.

Specifically, the Examiner objects to Claim 4 in that the recitation of a "method based on claims 1-2" is confusing because it is unclear if the method requires the step of both claims 1 and 2 or requires the steps of either claim 1 or 2." Claim 4 has been amended to recite "the method of Claim 1 or 2," thereby requiring the steps of either Claim 1 or 2 rather than the steps of both Claims 1 and 2.

Applicants respectfully submit that the rejection of Claims 1-4 under 35 U.S.C. § 112, second paragraph, is obviated in view of the amendment to Claim 4. Accordingly, Applicants respectfully request its withdrawal.

#### **B. The Rejection of Claims 1-4 Under the Judicially Created Doctrine of Obviousness-type Double Patenting**

Claims 1-4 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 1-5 of U.S. Patent No. 6,365,375 B1. Applicants respectfully request that this rejection be held in abeyance until the allowable subject matter of the instant application is determined, at which time Applicants propose to file a Terminal Disclaimer, or take other appropriate action.

**C. The Rejection of Claims 1-4 Under 35 U.S.C. § 103(a)**

Claims 1-4 stand rejected under 35 U.S.C. § 103(a) as obvious over Zhang *et al.*, *Proc. Nat. Acad. Sci.* 89:5847-5851 (“Zhang”), in view of Sorge *et al.*, U.S. Patent No. 5,556,772 (“Sorge”). The rejection is respectfully traversed on the grounds that the PTO has failed to establish a *prima facie* case of obviousness.

**1. The Legal Standard.**

To reject a claim as under 35 U.S.C. § 103(a), the PTO bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *See In re Bell*, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the PTO cannot establish a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent. *See In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). The PTO must meet a three-part test to render a claimed invention *prima facie* obvious.

To begin with, the prior art references cited by the PTO must provide “motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant.” *See In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination rests relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 51 U.S.P.Q.2d 1386 (Fed.Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problem to be solved. *See id.*

However, the mere fact that the prior art could be modified to produce the claimed invention does not make the modification obvious unless the prior art also suggests the desirability of the modification. *See In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984). Rigorous application of the requirement for a showing of such motivation to combine

references is the best defense against the subtle but powerful attraction of an impermissible hindsight-based obviousness analysis. See *In re Dembiczak*, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). “Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor’s disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight.” See *id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. See *In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant’s disclosure. See *id.*

Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. See *In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). If any one of these three factors is not met, the PTO has failed to establish a *prima facie* case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

**2. There is no Motivation or Suggestion to Combine Zhang with Sorge.**

The PTO asserts that it would have been *prima facie* obvious to one of ordinary skill in the art “to utilize the polymerase moieties of *Sorge* in the method of *Zhang*” because *Sorge* teaches that “the amplification reaction is carried out using specific primers and the combination of the DNA polymerases produce a significant and unexpected amount of product cDNA products.”

Claim 1 of the present invention recites a method for the amplification of nucleic acid fragments from a sample, said method comprising first and second thermocyclic amplification reactions, wherein said first amplification reaction is carried out using completely randomized primers, said second amplification reaction is carried out using specific primers, and said first and second amplification reactions are carried out using the same mixture of at least two DNA polymerases, at least one of which possesses 3'-5' exonuclease activity. Claims 2-4 depend from Claim 1, thereby incorporating every limitation of Claim 1.

As described by the PTO, *Zhang* teaches a method for amplifying nucleic acid sequence fragments using two amplification reactions, wherein the first uses random primers and Taq polymerase, and the second uses specific primers and Taq polymerase.

The PTO correctly notes that Taq polymerase does not possess 3'-5' exonuclease activity. The PTO also describes *Zhang* as teaching multiple thermoamplification cycles and polymerase extension, but concedes that *Zhang* does not teach the use of two DNA polymerases.

The PTO describes *Sorge* as teaching a method for amplifying nucleic acid sequence fragments using a mixture of two enzymes, the first of which possesses substantial 3'-5' exonuclease activity and the second of which does not possess substantial 3'-5' exonuclease activity. Applicants believe that the PTO further characterizes *Sorge* as teaching that the disclosed method may be used to provide alternate methods for synthesizing polynucleotides such as DNA, that the disclosed methods use PCR, and that thermostable enzymes are preferably used in the disclosed methods.

Applicants respectfully submit that the PTO has not met its burden to show that the cited references provide suggestion or motivation to combine the teachings of *Sorge* with *Zhang*. There is simply no suggestion in either *Sorge* or *Zhang* that the DNA polymerases of *Sorge* should be used in the method of whole genome amplification of *Zhang* as alleged by the PTO. If the PTO is relying on facts within its personal knowledge to provide the suggestion or motivation to combine the teachings of *Sorge* and *Zhang*, Applicants respectfully request that the PTO explicitly provide such facts in an affidavit pursuant to 37 C.F.R. § 1.104(d)(2).

In particular, neither *Sorge* nor *Zhang* teach or suggest that the DNA polymerases of *Sorge* would be more useful in whole genome amplification than any other improvement to the art of nucleic acid amplification. The art of nucleic acid amplification includes a myriad of methods and compositions for, *inter alia*, increasing the yield or extending the length of amplification products, increasing the fidelity of amplification or amplifying particular sequences. Such methods include, for example, varying the concentrations of reagents, mutating polymerases to introduce desirable characteristics, shortening or extending primer lengths, and the like. Any or all of these methods could conceivably be used to improve the method of whole genome amplification described by *Zhang*. Nothing in either *Sorge* or *Zhang* suggests that the composition of two polymerases disclosed by *Sorge*, as opposed to any other method or composition known by one of skill in the art to result in similar effects, should be used in whole genome amplification.

For example, *Zhang* uses random primers to initiate the first amplification reaction, and subsequently uses specific primers to amplify target sequences from the pool of

sequences amplified in the first reaction. *Sorge* in no way teaches or suggests that its two polymerases may be advantageously utilized when nucleic acid synthesis is initiated with random primers. *Sorge* also does not teach or suggest that its two polymerases can be utilized to amplify target sequences from a pool of sequences amplified by random primers. As *Sorge* does not teach or suggest either of the foregoing, it cannot teach or suggest that the same mixture of polymerases may be used to amplify both a first and a second amplification reaction, wherein the first is initiated with random primers and the second is initiated with specific primers. In fact, no teaching of *Sorge* suggests that the combination of polymerases disclosed therein would be more useful in the whole genome amplification method of *Zhang* than any other technique that purports to improve a nucleic acid amplification reaction. Thus, Applicants respectfully submit that there is no suggestion or motivation in *Sorge* to use the polymerases of *Sorge* in the method of whole genome amplification of *Zhang*.

Moreover, there is no suggestion or motivation in *Zhang* to use the polymerases of *Sorge* in the method of whole genome amplification of *Zhang*. *Zhang* suggests that the whole genome amplification method described therein could conceivably be improved by further changes in "primer length, primer-extension conditions, dNTP concentrations, or other aspects of the reaction." See *Zhang* at p. 5850, column 1, paragraph 2. Even this broad, nonspecific, precatory language does not teach or suggest that whole genome amplification can be improved using a mixture of two polymerases, one with and one without 3'-5' exonuclease activity. Rather, this teaching invites further experimentation regarding primer length and reaction conditions to determine whether changes to these variables can improve the disclosed method. *Zhang* does not even teach or suggest that the method could possibly be improved using a single polymerase with 3'-5' exonuclease activity, much less a mixture of two polymerases, one with and one without such activity. Thus, *Zhang* provides no teaching or suggestion that the whole genome amplification method disclosed therein can be improved by use of the DNA polymerases of *Sorge*. Accordingly, neither *Zhang* nor *Sorge* provide suggestion or motivation to use the DNA polymerases of *Sorge* in the whole genome amplification method of *Zhang*.

In fact, only Applicants' disclosure provides motivation to use the mixture of polymerases of *Sorge* in the whole genome amplification method of *Zhang*. The problems with *Zhang* recognized by Applicants include insufficient fidelity of amplification and the need for large amounts of starting material, both of which are ameliorated by use of a

mixture of two polymerases. *See* the specification at page 2, line 26 to page 3, line 18. Applicants, not *Sorge* or *Zhang*, teach that a mixture of two DNA polymerases may be used to remedy these defects in the whole genome amplification method of *Zhang*. However, using the Applicant's disclosure as a blueprint for piecing together the prior art to defeat patentability constitutes the essence of hindsight. As the PTO well knows, use of a hindsight-based obviousness analysis is strictly forbidden. *See In re Dembiczak*, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). Therefore, Applicants' own teachings cannot serve as a motivation or suggestion to use the DNA polymerases of *Sorge* in the whole genome amplification method of *Zhang*.

In support of its assertion of obviousness, the PTO quotes *Sorge* extensively, stating that

[a]lthough compositions comprising a DNA polymerase with less 3'-5' exonuclease activity than the enzyme possessing substantial 3'-5' exonuclease activity may produce superior results in a variety of synthesis experiments, the composition is especially useful in DNA synthesis where there exists one or more mismatched nucleotide(s), particularly mismatches at the 3' end of one or more synthesis primer(s). In such situations, the results achieved, *i.e.*, the amount of synthesis product produced, are significantly greater than the amount of synthesis product obtained using either a DNA polymerase with less 3'-5' exonuclease activity than the enzyme possessing substantial 3'-5' exonuclease activity or with a DNA polymerase possessing substantial 3'-5' exonuclease activity alone. Other advantages of the subject composition include increased synthesis product yield, increased transcription length, and the synthesis of polynucleotides that cannot be synthesized by a given DNA polymerase alone.

*See Sorge* at column three, lines 10 to 27. While Applicants concede *Sorge's* mixture of two polymerases, one with and one without 3'-5' exonuclease activity, has many advantages, none of the benefits cited by the PTO suggests that these polymerases should be used in a method of whole genome amplification as described by *Zhang*.

The quoted portion of *Sorge* suggests that longer amplification products may be generated in some circumstances by use of two DNA polymerases rather than only one.

However, as described above, the art of DNA amplification is rife with methods and compositions alleged to improve the length of amplification products. Applicants respectfully submit that nothing disclosed by *Sorge* suggests that use of two polymerases would be more useful to the method of *Zhang* than any other such method.

In addition, *Sorge*'s teaching that certain polynucleotides can be synthesized using two DNA polymerases but not by one DNA polymerase does not suggest that two polymerases should be used in the whole genome amplification method of *Zhang*. *Sorge* does not describe the characteristics of such polynucleotides, and there is no suggestion that such sequences are responsible for the deficiencies of the method of *Zhang*.

The PTO further alleges that the ability of *Sorge*'s mixture of polymerases to synthesize product nucleic acids when mismatches between the synthesis primer and the template prevent such synthesis by a single polymerase provides motivation to use the polymerases of *Sorge* in the whole genome amplification method of *Zhang*. However, there is no indication that mismatches between primers and target sequences present a significant problem in the whole genome amplification method of *Zhang*. Thus, the teaching provided by *Sorge* regarding these advantages of using two DNA polymerases, one with and one without 3'-5' exonuclease activity, would not suggest the use of two such DNA polymerases in the method of *Zhang*. Accordingly, Applicants respectfully submit that there is no motivation or suggestion to combine the teachings of *Zhang* and *Sorge*.

As there is no motivation or suggestion to combine *Zhang* with *Sorge*, Applicants respectfully submit that the PTO has not established a *prima facie* case of obviousness of the invention as presently claimed. Therefore, Applicants respectfully submit that the rejection of Claims 1-4 under 35 U.S.C. § 103(a) as obvious over *Zhang* in view of *Sorge* is erroneous and earnestly request its withdrawal.

### CONCLUSION

Applicants respectfully submit that Claims 1-9 satisfy all the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 1-9 to issuance is therefore kindly solicited.

No fees in addition to the petition fee are believed due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds U.S. Deposit Account No. 16-1150 (order no. 1803-330-999).



Respectfully submitted,

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Rahul Pathak

(Reg. No.)

For: Nikolaos C. George (39,201)

**PENNIE & EDMONDS** LLP  
1155 Avenue of the Americas  
New York, NY 10036-2711  
(212) 790-9090